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EXAMINER	
BAUGHMAN, MOLLY E	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/670,701	SU ET AL.	
	Examiner	Art Unit	
	Molly E. Baughman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,9-14 and 27-34* is/are pending in the application.

4a) Of the above claim(s) *4 and 27-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,7 and 9-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *7/1/08* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/25/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments to the specification and drawings, particularly providing sequence identifiers to sequences of more than 10 nucleotides in length, are acknowledged and accepted.

2. Applicant's arguments, see pg.6, filed 5/2/08, with respect to the rejection(s) of claim(s) 1-3, 5, 7, and 9-26 under 35 USC § 103 (Cleve et al. (1998) in view of Dimitrov et al. (US 2003/0013091) and further in view of Su et al. (US 7,019,828)), as well as claim(s) 1-3, 5, 7, and 9-26 under 35 USC § 103 (Singer et al. (US 6,534,266) in view of Urdea et al. (US 5,635,352) in view of Horn et al. (US 2001/0009760), and further in view of Su et al. (US 7,019,828)), have been fully considered and are persuasive since Su et al. is commonly owned by the assignee of the instant application. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Woudenberg (US 7,198,900); Hildebrandt et al., "Surface-Enhanced Resonance Raman Spectroscopy of Rhodamine 6G Absorbed on Colloidal Silver," J. Phys. Chem., 1984, Vol.88, pp.5935-5944; and Kudelski et al., "Characterization of the copper surface optimized for use as a substrate for surface-enhanced Raman scattering," Vibrational Spectroscopy 1998, Vol.16, pp.21-29.

3. Upon further consideration, new grounds of rejection are made under 35 U.S.C. 112.

4. Claims 1-3, 5, 7, and 9-14 are currently under examination.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-3, 5, 7, and 9-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 1-3, 5, 7, and 9-14 are confusing because independent claims 1 and 12 recite the limitation of the barcodes detected by a technique selected from the group consisting of fluorescent spectroscopy, raman spectroscopy, Fourier transform infrared spectroscopy (FTIR), and surface Plasmon resonance, however these claims also introduce the limitation of the barcodes being located proximately to a signal enhancing surface comprising a salt to enhance the signal. The applicants point to the specification on page [0122] for support, which discusses such signal enhancing surfaces only in the context of raman spectroscopy, so it is unclear how such detection occurs in fluorescent spectroscopy, Fourier transform infrared spectroscopy (FTIR), and surface Plasmon resonance. Clarification is required.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-3, 5, 7, and 9-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cleve et al. (Mol. Cell. Probes (1998) 12:243-147) in view of Dimitrov et al (U.S. 2003/0013091), and further in view of Hildebrandt et al., "Surface-Enhanced Resonance Raman Spectroscopy of Rhodamine 6G Absorbed on Colloidal Silver," J. Phys. Chem., 1984, Vol.88, pp.5935-5944, OR Kudelski et al., "Characterization of the copper surface optimized for use as a substrate for surface-enhanced Raman scattering," Vibrational Spectroscopy, 1998, Vol.16, pp.21-29.

Cleve teaches a method comprising: (a) obtaining a barcode comprising two or more tags attached to an organic molecule backbone (see page 245, columns 1 and 2, where the branched DNA amplifier molecule has 15 branches with four copies of a sequence which bind to labeled probes, where binding of the labeled probes will result in two or more tags attached in a noncovalent manner to an organic molecule backbone), (b) binding the barcode to a target (see page 245, column 2, where the

probes are hybridized to a target), (C) detecting the barcode bound to the target (see page 246, subheading "Flow Cytometry", where the barcodes are individually detected). Wherein the organic molecule backbone comprises one or more branched nucleic acids (see page 245, column 1 and 2, where branched nucleic acids with 15 branches are used which are organic molecules) and the barcode is detected by a technique of fluorescence spectroscopy (see figure 1, and page 246, column 1, where fluorescence spectroscopy is used to measure the beads).

With regard to claims 2-3, Cleve teaches single stranded nucleic acid probes (see page 245, columns 1 and 2, where the probes are single stranded).

With regard to claim 5, Cleve teaches the use of a fluorescent dye such as fluorescein (see page 246, column 2, where fluorescein is, of course, a fluorescent dye, but also will function as a Raman tag).

With regard to claim 7, Cleve teaches branched nucleic acids where the branches are at predetermined locations on the backbone (see page 245, columns 1 and 2).

With regard to claim 9, Cleve teaches that the barcode binds via the oligonucleotide probe (see page 245, column 2).

With regard to claims 11, 13, and 14, Cleve teaches a nucleic acid target and .detection of the binding to the target (see page 245, column 2).

Cleve does not teach the use of a plurality of barcodes on the branched DNA nor the situation where the number of barcodes exceeds the number of different types of tags.

Dimitrov expressly teaches the use of a plurality of barcodes since Dimitrov teaches that "Several unique combinations of labels can be formed using branched nucleic acids (see page 7, paragraph 0057)." Dimitrov further notes that "nucleic acids labeled with any or all of these combinations can be bound to another nucleic acid through hybridization (see page 7, paragraph 0055)."

Dimitrov further teaches the situation where the number of barcodes exceeds the number of different types of tags. Dimitrov expressly states "In this invention, various ratios of different label monomers bound to nucleic acids can be combined to generate a diverse population of unique labels that can include up to 1017 or more unique labels. For example, a nucleic acid labeled with two fluorescein labeled nucleotides and three rhodamine labeled nucleotides will emit light at a different wavelength compared to a nucleic acid labeled with three fluorescein nucleotides and two rhodamine nucleotides. In another example, a nucleic acid could be labeled with different ratios of three or more label monomer:nucleotides which greatly increases the variety of unique labels that can be generated" (see paragraph 0065). So Dimitrov expressly teaches the situation where ratios of different labels are combined to provide a much larger number of different tags. Dimitrov recognizes that up to 10^{17} or more unique labels can be formed by the use of ratios of a much small number of labels.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Cleve to use the multi-fluor branched DNA labels of Dimitrov since Cleve expressly motivates the use of different colors, stating "In addition, the principle of FCM quantitation can be expanded to take

advantage of the technology's unique strengths: through the use of software tools, beads of different colours or different sizes can be quantitated separately" (see page 244, column 1). Thus, Cleve directly motivates the use of different colors in the analysis assay and Dimitrov addresses this ability with the branched DNA-labels that can differ in color to "provide an accurate and sensitive system for the detection and quantitation of analytes in a mixture (see page 2, paragraph 10)." An ordinary practitioner would have been motivated to use the multifluor branched DNA probes of Dimitrov in the branched DNA assay of Cleve in order to permit multiplex detection of different analytes in a mixture as taught by Dimitrov and as motivated by Cleve, who desired to detect both HIV and cytomegalovirus (see page 2471 column 1, for example) in a single reaction.

Cleve also does not discuss the use of a signal enhancing surface comprising a salt located in proximity to the barcodes.

Hildebrandt et al. demonstrate that the use of a signal enhancing surface in proximity to label during raman spectroscopy. In his method, he demonstrates the use of various anions (Cl-, I-, Br-, F-, and SO_4^{2-} in the form of salts, i.e. HCl, NaCl, or KCl, see abstract and pg.5937, right column, 2nd paragraph from bottom) to enhance the signal of a fluorescent dye (Rhodamine 6G) in proximity to a signal enhancing surface (i.e. colloidal silver) 2-100 fold (see Figures 2 and 3, and Table 1).

Kudelski et al. describe a similar method to that of Hildebrandt, but instead use a copper surface during raman spectroscopy. Kudelski demonstrate applying various electrolytes to the copper surface (i.e. LiCl, KCl, KI, CuCl2, CuSO4, H2SO4) prior to

application of a target (i.e. pyridine), which is shown to enhance (or activate) the surface and increase the signal (see Fig.5, and Fig.9).

One of ordinary skill in the art would have been motivated to modify the method of Cleve et al., as modified by Dimitrov, to use Raman spectroscopy during detection where the barcodes are proximately located to a signal enhancing surface comprising a salt because Raman spectroscopy was a conventional detection method at the time of the invention for detection of various labels, as demonstrated by both Hildebrandt and Kudelski. Furthermore, both Hildebrandt and Kudelski, in different techniques and applications, demonstrate how the application of a salt to the surface of a signal enhancing surface can increase signals during Raman spectroscopy 2-100 fold. Since Cleve and Dimitrov demonstrate the benefits of using a plurality of barcodes, as taught by claims 1 and 12, during the detection of a target, and Hildebrandt and Kudelski each demonstrate that it was conventional in the art at the time of the invention to use salts with a signal enhancing surface in order to enhance or amplify the signal during Raman spectroscopy, it would have been obvious to one skilled in the art to substitute one detection method for the other to achieve the predictable result of enhancing the signal from the plurality of barcodes during detection.

11. Claims 1-3, 5, 7, 9-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singer et al (U.S. Patent 6,534,266) in view of Urdea et al (U.S. Patent 5,635,352), in view of Horn et al (U.S. 2001/0009760), and further in view of Hildebrandt et al., "Surface-Enhanced Resonance Raman Spectroscopy of Rhodamine 6G Absorbed on Colloidal Silver," J. Phys. Chem., 1984, Vol.88, pp.5935-5944, OR Kudelski et al.,

"Characterization of the copper surface optimized for use as a substrate for surface-enhanced Raman scattering," Vibrational Spectroscopy, 1998, Vol.16, pp.21-29.

Singer teaches a method of claims 1 and 12 comprising: (a) obtaining a plurality of barcodes, at least one of the plurality of barcodes comprising two or more different tags attached to an organic molecule backbone (see column 8, lines 6-38, where oligonucleotides have five different fluorophores attached to the nucleic acid probe backbone to form 31 different barcodes), (b) binding at least one of the plurality of barcodes to a target (see column 8, • lines 39-43, where the probes are hybridized to a target), (c) detecting at least one of the plurality of barcodes bound to the target (see column 8, lines 44-57, where the barcodes are individually detected). Wherein the barcodes are detected by fluorescence spectroscopy (see column 9, lines 5-20) and wherein the number of barcodes in the plurality of barcodes exceed the number of different types of tags attached to the plurality of barcodes (see column 8, lines 16-24, "Using a total of five spectrally distinguishable fluorochromes, 31 different bar codes are created without using a given fluorochrome more than once in a given bar code. The creation of the 31 bar codes using 5 fluorochromes is an extension of the scheme illustrated in FIG. 1, where 15 qualitative bar codes are created using 4 fluorochromes. One of the 31 bar codes is assigned to each of the 31 target sequences.").

With regard to claims 2-3, Singer teaches single stranded nucleic acid probes (see column 8, lines 16-38, where the oligonucleotides were synthesized, which necessarily is single stranded).

With regard to claim 5, Singer teaches the use of a variety of fluorescent dyes such as Cy3, Cy5, etc (see column 3, lines 1-2, where these dyes are, of course, fluorescent dyes, but also will function as Raman tags).

With regard to claim 9, Singer teaches that the barcode binds via the oligonucleotide probe (see column 8, lines 39-43).

With regard to claim 10, Singer teaches that distinguishable barcodes can be generated using multiple copies of the same tag (see column 3, line 59 to column 4, line 6).

With regard to claims 11, 13, and 14, Singer teaches a nucleic acid target and detection of the binding to the target (see column 8, lines 39-57).

Singer does not teach the use of branched DNA probes.

Urdea teaches a method of claims 1 and 12 comprising: (a) obtaining a barcode comprising two or more tags attached to an organic molecule backbone (see figure 11 and column 20, line 35 to column 21, line 49, where the AMP or comb probe is formed by the attachment of branches of nucleotides, and where 14 different tags are attached to the nucleic acid backbone (see column 20, line 38, specifically)), (b) binding the barcode to a target (see figure 11 and column 21, line 50 to column 22, line 7, where the probes are hybridized to a target), (c) detecting the barcode bound to the target (see figure 11 and column 22, lines 8-20, where the barcodes are detected).

With regard to claims 2-3, Urdea teaches single stranded nucleic acid probes (see figure 11 and column 20, line 35 to column 21, line 37, where the oligonucleotides were synthesized, and shown as single stranded).

With regard to claim 5, urdea teaches the use of nucleotide tags which are detected (see figure 11 and columns 20-22).

With regard to claims 6-7, Urdea teaches branched nucleic acids with branches located at predetermined sites along the backbone (see figure 11 and column 20, line 35 to column 21, line 40).

With regard to claim 9, Urdea teaches that the barcode binds via the oligonucleotide probe (see figure 11 and Column 21, line 50 to column 22, line 7).

With regard to claim 10, Urdea teaches that distinguishable barcodes can be generated using multiple copies of the same tag (see figure 13, where binding of AMP 1 and AMP2 can be distinguished by LP1 and LP2).

With regard to claims 11, 13, 14, Urdea teaches a nucleic acid target and detection of the binding to the target (see figures 11 and 13 and column 21, line 50 to column 22, line 7).

With regard to claim 12, Urdea teaches a "container" and "probe section" where the tagged LP1 and LP2 probes are hybridized to the AMP probes to create a barcode (see figure 13).

Horn provides a specific motivation to apply the branched DNA (or bDNA) method of Urdea to in situ hybridization methods such as those of Singer (see paragraph 0110-0111).

It would have been prima facie obvious to one of ordinary skill in the art at the. time the invention was made to modify the method of Singer to use the sensitive branched DNA probes of Urdea as motivated by Urdea and Horn since Singer

recognizes a need for sensitive detection, noting "An imaging technology, preferred for sensitive, quantitative detection of fluorochromes is described in Femino (see column 6, lines 32-34). Urdea notes regarding Branched DNA probes that "The invention increases both the sensitivity and specificity of such assays, by reducing the incidence of signal generation that occurs in the absence of target, and does not involve a substantial increase in either time or cost relative to current assay configurations (see column 2, lines 46-51)." Consequently, Urdea informs the ordinary practitioner that branched DNA probes are desirable for a number of reasons including sensitivity and specificity and reduction in nonspecific signal and these are elements of interest to Singer, who is interested in sensitive quantitative detection in an in situ assay. Horn specifically motivates the use of branched DNA probes in *in situ* assays such as those employed by Singer, noting "These results demonstrate the usefulness of bDNA in mapping small regions of DNA on a large backbone. Not only was the time to completion greatly shortened using bDNA (1 day or less) but the fluorescence signal using bDNA was considerably higher (see paragraph 0111)." So an ordinary practitioner, interested in sensitive detection using the bar code method of Singer, would have been motivated to further amplify the signal of the bar codes with branched DNA since Urdea indicated that branched DNA improved sensitivity and Horn expressly indicates that branched DNA use in *in situ* hybridization assays shortened the time to completion while also providing considerably greater fluorescence signal.

Singer also does not discuss the use of a signal enhancing surface comprising a salt located in proximity to the barcodes.

Hildebrandt et al. demonstrate that the use of a signal enhancing surface in proximity to label during raman spectroscopy. In his method, he demonstrates the use of various anions (Cl-, I-, Br-, F-, and SO_4^{2-} in the form of salts, i.e. HCl, NaCl, or KCl, see abstract and pg.5937, right column, 2nd paragraph from bottom) to enhance the signal of a fluorescent dye (Rhodamine 6G) in proximity to a signal enhancing surface (i.e. colloidal silver) 2-100 fold (see Figures 2 and 3, and Table 1).

Kudelski et al. describe a similar method to that of Hildebrandt, but instead use a copper surface during raman spectroscopy. Kudelski demonstrate applying various electrolytes to the copper surface (i.e. LiCl, KCl, KI, CuCl2, CuSO4, H2SO4) prior to application of a target (i.e. pyridine), which is shown to enhance (or activate) the surface and increase the signal (see Fig.5, and Fig.9).

One of ordinary skill in the art would have been motivated to modify the method of Singer et al., as modified by Urdea and Horn, to use Raman spectroscopy during detection where the barcodes are proximately located to a signal enhancing surface comprising a salt because Raman spectroscopy was a conventional detection method at the time of the invention for detection of various labels, as demonstrated by both Hildebrandt and Kudelski. Furthermore, both Hildebrandt and Kudelski, in different techniques and applications, demonstrate how the application of a salt to the surface of a signal enhancing surface can increase signals during Raman spectroscopy 2-100 fold. Since Singer et al., Urdea et al. and Horn et al. demonstrate the benefits of using a plurality of barcodes, as taught by claims 1 and 12, during the detection of a target in situ, and Hildebrandt and Kudelski each demonstrate that it was conventional in the art

at the time of the invention to use salts with a signal enhancing surface in order to enhance or amplify the signal during Raman spectroscopy, it would have been obvious to one skilled in the art to substitute one detection method for the other to achieve the predictable result of enhancing the signal from the plurality of barcodes during in situ detection.

12. Claims 1-3, 5, 7, and 9-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woudenberg (US 7,198,900, filed 8/29/03), in view of Hildebrandt et al., "Surface-Enhanced Resonance Raman Spectroscopy of Rhodamine 6G Absorbed on Colloidal Silver," J. Phys. Chem., 1984, Vol.88, pp.5935-5944, OR Kudelski et al., "Characterization of the copper surface optimized for use as a substrate for surface-enhanced Raman scattering," Vibrational Spectroscopy, 1998, Vol.16, pp.21-29.

Regarding claims 1 and 12-14, Woudenberg teaches a method comprising:

(1) obtaining a plurality of barcodes, at least one of the plurality of the barcodes comprising two or more different types of tags attached to an organic molecule backbone *(see Figure 1A, particularly barcodes "1P1," "2P2A," and "2P2B," each comprising two or more different types of tags attached to an organic backbone; see also Fig.6A, 8A-B, 12A; col.1, lines 58-62; col.2, lines 4-20; col.3, lines 33-38; col.6, lines 55-67; col.7, lines17-18; col.16, lines 44-67)*;

(2) binding at least one of the plurality of barcodes to a target *(see Figure 1A after "Denature/Anneal")*; and

(3) detecting the at least one of the plurality of barcodes bound to the target (Figure 1A, after SMD - single molecule detection),

wherein the organic molecule backbone comprises one or more branched nucleic acids *(Woudenberg teaches this in two different ways - (1) see Figure 1A, the curvy line and jagged lines (i.e. identity portions of the probes) representing a branched point of the organic backbone from the reaction portion of the probe, as exemplified in the instant disclosure's Figure 1, labeled 120 - see also col.3, lines 12-30 and col.20-22 for description of probes; and (2) he teaches the coded molecular tag portion of the probe also comprising a mobility modifier, which can be a nucleic acid polymer having a branched architecture, see col.11-12, particularly col.12, line 32)* and the at least one of the plurality of barcodes is detected by a technique selected from the group consisting of fluorescent spectroscopy, Raman spectroscopy, Fourier transform infrared spectroscopy (FTIR), and surface plasmon resonance *(see col.31, lines 25-63, which lists fluorescent spectroscopy, Raman spectroscopy, and surface plasmon resonance as detection techniques)*,

wherein the number of barcodes in the plurality of barcodes exceed the number of different types of tags attached to the plurality of barcodes *(see Fig.4B-D and col.23, lines 15-55, where there are multiple molecular complexes comprising different analytical portions, but the same code of different tags)*.

Regarding claim 2, Woudenberg teaches the method wherein the backbone comprises at least one molecule selected from the group consisting of a nucleic acid, a

peptide, a polysaccharide, a bio-polymer and a synthetic polymer (see col.6, lines 55-67, where the molecular tag is a nucleic acid sequence or amino acid sequence).

Regarding claim 3, Woudenberg teaches the method wherein the nucleic acid is single-stranded DNA (see col.3, line 35, oligonucleotide).

Regarding claim 5, Woudenberg teaches the method wherein the tag is selected from the group consisting of nucleic acids, nucleotides, nucleotide analogs, base analogs, fluorescent dyes, peptides, amino acids, modified amino acids, organic moieties, Raman tags, quantum dots, carbon nanotubes, fullerenes, submicrometer metal particles, electron dense particles and crystalline particles (see col.16, lines 44-67).

Regarding claim 7, Woudenberg teaches the method wherein the branches are located at predetermined sites along the backbone (see Figure 1A, where the branched portion is on the terminal end of the barcode or probe).

Regarding claim 9, Woudenberg teaches the method wherein the barcode binds to the target via a probe moiety (see Figure 1A, after "Denature/Anneal," also the "analytical portion" of the probe/barcode described in the specification, mentioned above).

Regarding claim 10, Woudenberg teaches the method wherein distinguishable barcodes are generated by attachment of the same tag to different sites along the same backbone (see Figure 1A, 8A-B, and col.7, lines 12-13).

Regarding claim 11, Woudenberg teaches the method wherein the target is selected from the group consisting of a protein, a peptide, a glycoprotein, a lipoprotein,

a prion, a nucleic acid, a polynucleotide, an oligonucleotide, a lipid, a fatty acid, a carbohydrate, a glycolipid, a phospholipid, a sphingolipid, a lipopolysaccharide, a polysaccharide, a eukaryotic cell, a prokaryotic cell, a bacterium, a phage, a virus and a pathogen (see col.13, lines 44-67).

Even though Woudenberg teaches Raman spectroscopy as a detection technique, he does not teach the method wherein the barcodes are proximately located to a signal enhancing surface comprising a salt selected from the group consisting of LiF, NaF, KF, LiC1, NaC1, LiBr, NaBr, LiI, NaI, and KI, the location sufficiently proximal to enhance the signal 2-100 fold.

However, both Hildebrandt and Kudelski demonstrate that the use of signal enhancing surfaces comprising salts in raman spectroscopy was a conventional technique in the art at the time of the invention for enhancing the signal during detection. In further detail, Hildebrandt et al. demonstrates the use of various anions (Cl-, I-, Br-, F-, and SO_4^{2-} in the form of salts, i.e. HCl, NaCl, or KCl, see abstract and pg.5937, right column, 2nd paragraph from bottom) to enhance the signal of a fluorescent dye (Rhodamine 6G) in proximity to a signal enhancing surface (i.e. colloidal silver) 2-100 fold (see Figures 2 and 3, and Table 1). Kudelski et al. describe a similar method to that of Hildebrandt, but instead use a copper surface during raman spectroscopy. Kudelski demonstrate applying various electrolytes in the form of salts to the copper surface (i.e. LiCl, KCl, KI, CuCl2, CuSO4, H2SO4) prior to application of a target (i.e. pyridine), which is shown to enhance (or activate) the surface and increase the signal (see Fig.5, and Fig.9).

One of ordinary skill in the art would have been motivated to modify the method of Woudenberg et al. to use a signal enhancing surface comprising a salt during detection because Woudenberg demonstrates the benefits of using Raman Spectroscopy as a detection technique, and both Hildebrandt and Kudelski demonstrate that the use of signal enhancing surfaces comprising salts in raman spectroscopy was a conventional technique in the art at the time of the invention for enhancing the signal during detection. Therefore, the skilled artisan would have had a reasonable expectation of success in using a signal enhancing surface comprising a salt during Raman Spectroscopy in the method of Woudenberg et al. in order to increase the signal from the plurality of barcodes and provide a more sensitive detection. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed signal enhancing surface comprising a salt therein.

Summary

13. No claims are free of the prior art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Molly E. Baughman whose telephone number is (571)272-4434. The examiner can normally be reached on Monday-Friday 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637

/Molly E Baughman/
Examiner, Art Unit 1637